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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,823	10/23/2001	Francesco G. Salituro	VPI/99-01 CON US	1783

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,823	SALITURO ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 12/22/03. Applicant has amended claims 1 and 4-13. Applicant has canceled claims 2 AND 3. Claims 14-26 are new. Claims 1 and 14-23 are compound claims. Claim 4 is a composition claim. Claims 5-13 and 24-26 are use claims. The application concerns some 3-oximino indole compounds, compositions, and uses thereof.

Response to Amendment

2. Applicants amendments overcome all the formal objections made in points #3-#5 and #7 of the previous office action. Applicants' deletion of the superfluous material from claim 1 and cancellation of claim 3 overcomes the indefiniteness rejections made in points #8 and #9. Applicants amendments to the use claim 5 specifying that Applicants compounds are to be administered overcomes the indefiniteness and utility rejections made in point #10. Applicants' deletion of prevention overcomes the enablement rejection made in point #11. Applicants new provisos overcome the anticipation rejections over Esaki EP 685,463 A1) and Guerry (WO 96/16046 A1) made in points #14 and #15. However, those provisos are new matter as discussed below.

Oath/Declaration

3. The oath or declaration remains defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or

declaration is defective because: Non-initialed and/or non-dated alterations have been made to Applicant Wilke's address. See 37 CFR 1.52(c).

Applicants' remarks concerning the difficulty of locating Applicant Wilke are noted.

Claim Rejections - 35 USC § 112

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claim 24 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify which patients are to have their JNK3 inhibited. Is every patient to be so treated or just some of them? Is every Parkinson's disease sufferer to be treated or only those with elevated levels of JNK3? It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a enzyme inhibitor and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

5. Claims 5-13 remain rejected and claims 24 and 25 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Parkinson's disease, does not reasonably provide enablement for treating the multitude of diseases embraced by these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The issue is the correlation between clinical efficacy for clinical efficacy of disease treatment and Applicants' single *in vitro* assay. The factors to be considered in making an enablement rejection have been summarized previously. a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different claimed diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating claimed diseases, formulations, and dosages used is found in the passages cited above. There is a single *in vitro* assay described in the passage spanning line 17, page 125 to line 5, page 126. Applicants do not assert and it is not art recognized that this assay is correlated to clinical efficacy for treatment of any human disease.

c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in JNK3 related diseases is that no drugs working by this mechanism are currently in clinical use. Search of Medline reveals only two clinical reports concerning JNK3 inhibitors, one for Crohn's disease (Hommes et al, "Inhibition of stress-activated MAP kinases induces clinical improvement in moderate to severe Crohn's disease" Gastroenterology, 2002 Jan; 122(1), pages 7-14) and Bozyczko-Coyne (Curr Drug Target CNS Neurol Disord) which teaches that a clinical trial in Parkinson's is under way for the compound CEP-1347. No other disease are presently understood as treatable by such inhibitors.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the hundreds of thousands of compounds of formula I as well as the hundred of diseases embraced by the claims. Thus, the scope of claims is very broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants argue that no *prima facie* case for lack on enablement was made and refer to a discussion in the specification of a relationship between Applicants' assay and clinical efficacy. Presumably these are the papers listed on pages 2-4 of the specification. None of these references are of record and none are available to the Examiner. Applicants fail to point to any specific passages in these references where correlation between the assay employed by the Applicants and clinical efficacy for disease tretment is taught. From the titles, none of the references appear to concern any clinical results and thus, logically could not offer any correlation between Applicants' test and clinical efficacy. The references appear to be speculative, not to distinguish between diseases caused by JNK3 and those producing excess JNK3, and not to discuss correlations to clinical efficacy. It is unclear that any of the references even discuss Applicants' specific assay.

6. Claims 1 and 4-26 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The provisos in the next to last six lines of claim 1 lack description. Nowhere in the specification is such a relationship linking the description among radicals R^1-R^4 and Y described. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts."

Priority

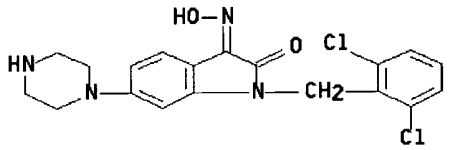
7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1 and 4-26 of this application. Applicants have expanded their definition of variables R^2-

R^6 from that given in Application 60/130,752. For example the definitions of R^2 and R^4 presently claimed have been expanded to include those broader claims of R^3 previously taught. Applicants have added –C(O)OR to the definition of R^2-R^4, which not previously taught. Applicants have added $N(O)_2$, NHOH, NO_2, and C(O)OR to the definition of R^5 and R^6. Thus, the effective filing date of the present claims is 4/21/00.

Claim Rejections - 35 USC § 102

8. Claims 1, 4, 5, and 13 remain rejected and claims 14, 15, and 17-23 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Gaeta (WO 99/65875 A1). The reference has a publication date of 12/23/99. The compound shown below fits formula (I) with $R^1 = R^2 = R^4$ = hydrogen, $R^3 = R^5$ = the non-aromatic heterocyclic ring piperazine, $Y = CH_2$-Q_1, and Q_1 = the substituted phenyl group 2,6-dichlorophenyl. It has Registry Number 252579-10-5 and is found in line 6, page 17 of the reference. It is called Compound XI. Biological activity is taught in line 19, page 25. See also claim 30. Compositions are taught in claim 29. Thus, Applicants claim 4 is anticipated. Claims 1, 2, 15, 16, and 22-28 of the reference teach cancer treatment with the above compounds. Thus, Applicants' claim 5 is anticipated. The testing protocol described in lines 6-11, page 27 uses the phrase "tumor masses". Thus, Gaeta (WO 99/65875 A1) possessed the concept

of treating solid tumors with the compounds above and Applicants claim 13 is anticipated.



9. Claim 24 is newly rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gaeta (WO 99/65875 A1) as discussed above. The reference does not teach inhibiting JNK3 kinase in a patient. However, it does teach treating tumors in a patient, albeit by a different mechanism. Applicants state in the passage spanning line 23, page 3 to line 7, page 4 that inhibiting JNK3 kinase in cancer patients will treat the cancer. Thus, it is inherent in the reference that the teaching of tumor treatment is a teaching of JNK3 inhibition. Just as the discovery of a new property does not make an old compound patentable, so does the discovery a new mechanism of action make an old use patentable. *Ex parte Novitski* 26 USPQ2d 1389. A process claim is anticipated even if patentee of prior art did not recognize that an "inventive concept" of the new claim was necessarily present, not merely probably or possibly present, in the prior art, *Verdegaal Brothers Inc. v. Union Oil Company of California* 2 USPQ2d 1051. *Mehl/Biophile International Corp. v. Milgraum* 52

USPQ2d 1303, "[i]nherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art."

Applicants rely upon their earlier claimed priority date to overcome this art. However, that claim has been denied.

Conclusion

10. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts

to reach the Examiner by telephone are unsuccessful, please contact Mukund Shah SPE of 1624 at (571)-272-0674.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK/me